REMARKS

Discussion of Claim Amendments

Claims 21-23, 25, and 28 have been amended to expedite the prosecution of this application and to further sharpen the claim language. In the Amendment filed on November 8, 2001 applicant added claims 21-31 and 33-37. In the "REMARKS" section, applicant inadvertently indicated that "claims 21-37 will be active in the application subsequent to entry of this amendment", at page 5, lines 1-2. Claim 32 was not provided.

Applicants have now renumbered previous claims 33-37 as present claims 32-36, respectively. The claim dependency also has been amended consistent with the new numbering scheme. Claim 36 includes a reference to "intravenous". New claims 37-62 have been added and are directed to embodiments of the invention. No new matter has been added.

The Office Action

The Office Action sets forth the following grounds for rejection: (1) claims 21-36 (as renumbered) are rejected under 35 U.S.C. § 103(a), as allegedly unpatentable over U.S. Patent 5,858,410 (Muller et al.) in view of U.S. Patent 5,360,593 (Bapatia); (2) claims 21-36 are rejected under 35 U.S.C. § 112, second paragraph, for an alleged indefiniteness; and (3) the disclosure is objected to for certain alleged informalities.

The Present Invention

The present invention is directed to an aqueous suspension comprising surface stabilized drug particles. Claims 21-62 are currently pending. A set of pending claims is attached.

Discussion of Obviousness Rejection

Claims 21-36 are rejected under 35 U.S.C. § 103(a), as allegedly unpatentable over Muller et al. in view of Bapatia. The Office Action contends that it would have been obvious to one of ordinary skill in the art to sterilize the composition of Muller et al. under nitrogen to achieve a beneficial effect of preventing oxidation of the active agent in view of Bapatia. Applicant respectfully traverses this rejection.

The Office Action has failed to make a *prima facie* case for obviousness. Bapatia relates to heat sterilization of bulk solids such as pharmaceuticals, foodstuffs, and cosmetics. Bapatia teaches that the bulk solids are protected from oxidative degradation from ambient atmospheric oxygen during heat sterilization by conducting the heating step while the solids are situated in a flux of an inert gaseous medium comprising nitrogen (column 1, lines 58-68). Further, in column 2, lines 52-64, Bapatia teaches that moisture must be avoided. Bapatia teaches that

"moisture leads to partial degradation of tobramycin". Bapatia teaches that dried tobramycin is sterilized for a minimum of 8.3 hours at a 130°C-135°C.

Bapatia teaches away from the present invention. The presently claimed invention, in contrast, relates to an aqueous suspension (i.e., one that contains water) which is sterilized under a nitrogen atmosphere. Water is a requirement in the presently claimed invention. In contradistinction, water must be avoided in Bapatia.

In view of the foregoing, there is no motivation to combine Bapatia and Muller et al. Motivation to combine Muller et al. and Bapatia, if any, can come only from a hindsight reconstruction employing applicants' invention as a road map. Hindsight reconstruction is impermissible under the law. Even if Muller et al. and Bapatia are combined, the combination does not suggest to those of ordinary skill in the art, the presently claimed invention.

In view of the foregoing, the obviousness rejection of claims 21-36 should be withdrawn. Claims 37-62 also should not be rejected on this basis.

Discussion of Indefiniteness Rejection

The amendment to claims 21-22 render this rejection moot. Further, applicant respectfully submits that the use of the term "substantially" does not render claims 21-22 vague.

The degree of precision necessary to satisfy § 112, second paragraph, is a function of the subject matter. *Miles Laboratories, In., v. Shandon, Inc.*, 997 F.2d 870, 27 USPQ2d 1123 (Fed. Cir. 1993), *cert. denied*, 510 U.S. 110 (1994). Claims are often drafted using terminology that is not numerically precise. As long as the result complies with the statutory requirement, that practice is permissible. *PPG Industries v. Guardian Industries Corp.*, 156 F.3d 1351, 48 USPQ2d 1351 (Fed. Cir. 1998). The term "substantially" is a descriptive term commonly used in patent claims to "avoid a strict numerical boundary to the specified parameter." *Pall Corp. v. Micron Seps.*, 36 USPQ2D 1225, 1229 (Fed. Cir. 1995). Terms such as "substantially" are "ubiquitous in patent claims." *Andrew Corp. v. Gabriel Electronics, Inc.*, 847 F.2d 819, 6 USPQ2d 2010 (Fed. Cir. 1988), *cert. denied*, 488 U.S. 927 (1988). See also *Ecolab Inc. v. Envirochem Inc.*, 60 USPQ2d 1173 (Fed. Cir. 2001) ("substantially uniform" avoids the strict 100% nonuniformity boundary).

The nature of the subject matter recited in claims 21-22 is such that the use of "substantially" is fully justified. There is no need to provide a percent value. In view of the foregoing, the indefiniteness rejection of claims 21-22 should be withdrawn. Claims 37-62 also should not be rejected on this basis.

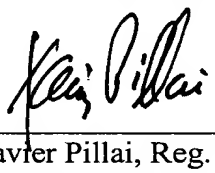
Discussion of Objection to Disclosure

Applicant's amendment to the specification renders this objection moot. In view of the foregoing, the objection to disclosure should be withdrawn.

Conclusion

The application is considered in good and proper form for allowance. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned attorney.

Respectfully submitted,



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Date: June 10, '02

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

AWADHESH K. MISHRA

Application No. 09/321,766 Art Unit: 1617

Filed: May 28, 1999 Examiner: E. J. Webman

For: THERMOPROTECTED COMPOSITIONS AND PROCESS FOR TERMINAL STEAM STERILIZATION OF MICROPARTICLE PREPARATIONS

AMENDMENTS TO SPECIFICATION AND CLAIMS MADE IN RESPONSE TO OFFICE ACTION DATED JANUARY 8, 2002

Amendments to the paragraph beginning at page 3, line 8:

The "thermoprotecting agents" and "thermoprotecting conditions" are characterized by their ability to restrict the increase in volume weighted mean diameter of the particulate suspension during and after terminal steam sterilization to a limit that the steam sterilized suspension can be injected by intravenous or other parenteral routes of administration without compromising the safety of the subject. A volume weighted mean diameter of up to about 3 μm ~~may~~ is considered safe for intravenous injection. However, such a suspension should not contain more than 3000 particles of 10 μm or greater size and not more than 300 particles of 25 μm or greater size according to the USP particulate test criterion. We have thus defined the term "successful steam sterilization" as a process with which one can prepare formulations which ~~does~~ do not contain particles of above specified diameter limits or preferably the volume weighted mean particle diameter of the suspension does not increase after steam sterilization by more than about two-times.

Amendment to the paragraph beginning at page 3, line 20:

While the surface modifiers possibly adsorb to the freshly made surfaces of drug particles during the process of particle size reduction, and (a) convert the lipophilic drug surface to a hydrophilic surface that has increased stability, and (b) possibly modify the surface charge of the drug particle surfaces, the thermoprotecting agent and thermoprotecting

conditions described herein help maintain the particle size distribution of the suspension during and after the terminal steam sterilization conditions.

Amendments to existing claims:

21. (Amended) An autoclavable composition of an aqueous injectable terminally steam sterilized suspension in a vial sealed under nitrogen atmosphere, said suspension containing particles of a water insoluble or poorly soluble biologically active substance with a volume weighted mean particle size of up to 3 μm ~~with not more than 3000 particles of 10μm or greater size and more than 300 particles of 25 μm or greater size~~, said particles surface stabilized with one or more phospholipid surface ~~modifier~~ modifiers, and a pharmaceutically acceptable amount safe for parenteral administration of a pharmaceutically acceptable, water soluble polyhydroxy thermoprotecting agent selected from the group consisting of ~~one or a combination of~~ trehalose, lactose, dextrose, sorbitol, dextran, ~~trehalose and~~ mannitol and mixtures thereof, ~~wherein the pH of said suspension is between 5 to 9,~~ the ratio of said active substance to said surface modifier is 1:1 to 5:1, and the amount of said surface modifier is in the range from 0.2% w/w to 5.0% w/w, wherein said composition is substantially completely devoid of surfactants that require during terminal steam sterilization elevation of their cloud point temperature by addition of a cloud point modifier, said composition is substantially devoid of surfactant additives which coagulate on steam sterilization, and said volume weighted mean particle size is not increased more than two-fold during and after terminal steam sterilization.

22. (Amended) An autoclavable composition of an injectable non-flocculating aqueous terminally steam sterilized suspension under nitrogen in a sealed vial, said suspension containing particles of a water insoluble or poorly soluble drug substance with a volume weighted mean particle size of up to 3 μm ~~with not more than 3000 particles of 10 μm or greater size and not more than 300 particles of 25 μm or greater size~~, said particles surface stabilized with one or more phospholipid surface ~~modifier~~ modifiers, and a pharmaceutically acceptable amount safe for parenteral administration of a pharmaceutically acceptable, water soluble polyhydroxy thermoprotecting agent, ~~wherein the pH of said suspension is between 5 to 9,~~ the ratio of said drug substance to said surface modifier is 1:1 to 5:1, the amount of said surface modifier is in the range from 0.2% w/w to 5.0% w/w, and said volume weighted mean particle size is not increased more than two-fold during and after terminal steam sterilization, and wherein said composition is substantially completely devoid of surfactants that require during terminal steam sterilization elevation of their cloud point temperature by

addition of a cloud point modifier and substantially devoid of surfactant additives which coagulate on steam sterilization.

23. (Amended) The composition of claim 21 or claim 22, wherein the suspension also includes ~~an amount of~~ a non-surfactant ~~additives such that the suspension attains an~~ additive to adjust osmotic pressure ~~safe for parenteral administration~~.

25. (Amended) The composition of claim 22, wherein the polyhydroxy compound is selected from the group consisting of ~~one or a combination of~~ trehalose, lactose, dextrose, sorbitol, dextran, ~~trehalose and~~ mannitol, and mixtures thereof.

28. (Amended) The composition of claim 22, wherein the suspension also contains a pharmaceutical ~~excipients~~ excipient for ophthalmic, peroral, or transdermal administration of the water insoluble or poorly soluble ~~active~~ drug substance.

~~33~~ 32. (Amended) The composition of claim 21, wherein the active substance is a sterol.

~~34~~ 33. (Amended) The composition of claim ~~33~~ 32, wherein the sterol is alfaxalone.

~~35~~ 34. (Amended) A lyophilized or spray dried powder prepared from the composition of claim 22.

~~36~~ 35. (Amended) A composition according to claim 22, wherein the water-insoluble or poorly water-soluble drug substance is suitable for either immediate release or sustained release delivery of said drug substance by parenteral administration.

~~37~~ 36. (Amended) The composition of claim ~~36~~ 35, wherein the parenteral administration is intramuscular, intravenous, or subcutaneous administration.

PATENT
Attorney Docket No. 401730/SKYEPHARMA

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

AWADHESH K. MISHRA

Application No. 09/321,766 Art Unit: 1617

Filed: May 28, 1999 Examiner: E. J. Webman

For: THERMOPROTECTED COMPOSITIONS AND PROCESS FOR TERMINAL STEAM STERILIZATION OF MICROPARTICLE PREPARATIONS

PENDING CLAIMS AFTER AMENDMENTS MADE IN RESPONSE TO OFFICE ACTION DATED JANUARY 8, 2002

21. An autoclavable composition of an aqueous injectable terminally steam sterilized suspension in a vial sealed under nitrogen atmosphere, said suspension containing particles of a water insoluble or poorly soluble biologically active substance with a volume weighted mean particle size of up to 3 μm, said particles surface stabilized with one or more phospholipid surface modifiers, and a pharmaceutically acceptable amount safe for parenteral administration of a pharmaceutically acceptable, water soluble polyhydroxy thermoprotecting agent selected from the group consisting of trehalose, lactose, dextrose, sorbitol, dextran, mannitol and mixtures thereof, the ratio of said active substance to said surface modifier is 1:1 to 5:1, and the amount of said surface modifier is in the range from 0.2% w/w to 5.0% w/w, wherein said composition is substantially completely devoid of surfactants that require during terminal steam sterilization elevation of their cloud point temperature by addition of a cloud point modifier, said composition is substantially devoid of surfactant additives which coagulate on steam sterilization, and said volume weighted mean particle size is not increased more than two-fold during and after terminal steam sterilization.

22. An autoclavable composition of an injectable non-flocculating aqueous terminally steam sterilized suspension under nitrogen in a sealed vial, said suspension containing particles of a water insoluble or poorly soluble drug substance with a volume weighted mean particle size of up to 3 μm, said particles surface stabilized with one or more phospholipid surface

modifiers, and a pharmaceutically acceptable amount safe for parenteral administration of a pharmaceutically acceptable, water soluble polyhydroxy thermoprotecting agent, the ratio of said drug substance to said surface modifier is 1:1 to 5:1, the amount of said surface modifier is in the range from 0.2% w/w to 5.0% w/w, and said volume weighted mean particle size is not increased more than two-fold during and after terminal steam sterilization, and wherein said composition is substantially completely devoid of surfactants that require during terminal steam sterilization elevation of their cloud point temperature by addition of a cloud point modifier and substantially devoid of surfactant additives which coagulate on steam sterilization.

23. The composition of claim 21 or claim 22, wherein the suspension also includes a non-surfactant additive to adjust osmotic pressure.

24. The composition of claim 21 or claim 22, wherein the suspension can be diluted with water for parenteral administration.

25. The composition of claim 22, wherein the polyhydroxy compound is selected from the group consisting of trehalose, lactose, dextrose, sorbitol, dextran, mannitol, and mixtures thereof.

26. The composition of claims 21 or claim 22, wherein the phospholipid surface modifier is selected from the group consisting of natural phospholipids and synthetic phospholipids.

27. The composition of claim 26 wherein the natural phospholipid is an egg phospholipid or soy phospholipid.

28. The composition of claim 22, wherein the suspension also contains a pharmaceutical excipient for ophthalmic, peroral, or transdermal administration of the water insoluble or poorly soluble drug substance.

29. The composition of claim 21, wherein the active substance is an antifungal agent.

30. The composition of claim 29, wherein the antifungal agent is intraconazole.

31. The composition of claim 21, wherein the active substance is an immunosuppressive agent.

32. The composition of claim 21, wherein the active substance is a sterol.

33. The composition of claim 32, wherein the sterol is alfaxalone.

34. A lyophilized or spray dried powder prepared from the composition of claim 22.

35.A composition according to claim 22, wherein the water-insoluble or poorly water-soluble drug substance is suitable for either immediate release or sustained release delivery of said drug substance by parenteral administration.

36. The composition of claim 35, wherein the parenteral administration is intramuscular, intravenous, or subcutaneous administration.

37. The composition of claim 31, wherein the immunosuppressive agent is a cyclosporin.

38. An aqueous suspension comprising particles of a water insoluble or poorly soluble biologically active substance, one or more surface modifiers, and a pharmaceutically acceptable, water soluble polyhydroxy thermoprotecting agent, sealed in a vial under nitrogen atmosphere, wherein the ratio of the active substance to the surface modifier and/or the thermoprotecting agent being selected so as to provide particle size stability during and after terminal steam sterilization, and the particle size subsequent to terminal steam sterilization is not more than about two-fold of the volume weighted mean particle size prior to the terminal steam sterilization.

39. An aqueous suspension comprising particles of a water insoluble or poorly soluble biologically active substance, one or more surface modifiers, and a pharmaceutically acceptable, water soluble polyhydroxy thermoprotecting agent, sealed in a vial under nitrogen atmosphere, the ratio of the active substance to the surface modifier and/or the thermoprotecting agent being selected to provide particle size stability during and after terminal steam sterilization wherein the particle size subsequent to terminal steam sterilization is not more than about two-fold of the volume weighted mean particle size prior to the terminal steam sterilization, wherein the suspension is substantially devoid of surfactants that require elevation of their cloud point temperature by addition of a cloud point modifier for further stabilization.

40. The suspension of claim 38, wherein the pH of the suspension before terminal steam sterilization is from about 5 to about 9.

41. The suspension of claim 38, which also includes a non-surfactant additive to adjust osmotic pressure of the suspension.

42. The suspension of claim 38, which also includes an amount of a non-surfactant additive such that, on diluting the suspension with a pharmaceutically acceptable diluent suitable for parenteral administration to a pharmaceutically acceptable concentration for parenteral administration, a suitable osmotic pressure of the diluted suspension results.

43. The suspension of claim 38, wherein the thermoprotecting agent is selected from the group consisting of trehalose, lactose, dextrose, sorbitol, dextran, mannitol, and mixtures thereof.

44. The suspension of claim 38, wherein the one or more surface modifiers are natural phospholipids or synthetic phospholipids.

45. The suspension of claim 44, wherein the natural phospholipid is an egg phospholipid or soy phospholipid.

46. The suspension of claim 38, wherein the amount of the surface modifier provides a biologically active substance to surface modifier ratio of up to 5:1.

47. The suspension of claim 38, wherein the amount of the surface modifier is in the range from about 0.2% w/w to about 5.0% w/w.

48. The suspension of claim 38, wherein the composition also contains a pharmaceutical excipient suitable for ophthalmic, peroral, or transdermal administration of the water insoluble or poorly soluble biologically active substance.

49. The suspension of claim 38, wherein the active substance is an antifungal agent.

50. The suspension of claim 49, wherein the antifungal agent is itraconazole.

51. The suspension of claim 38, wherein the active substance is an immuno-suppressive drug.

52. The suspension of claim 51, wherein the immuno-suppressive drug is a cyclosporin.

53. The suspension of claim 38, wherein the active substance is a sterol.

54. The suspension of claim 53, wherein the sterol is alfaxalone.

55. A lyophilized or spray dried powder prepared from the suspension of claim 38.

56. The suspension of claim 38, wherein the water-insoluble or poorly water-soluble biologically active substance is at a concentration suitable for either immediate release or sustained release delivery of the active substance by parenteral administration.

57. The suspension of claim 56, wherein the parenteral administration is intramuscular, intravenous, or subcutaneous administration.

58. A method for preparing an aqueous suspension comprising particles of a water insoluble or poorly soluble biologically active substance, one or more surface modifiers, and a pharmaceutically acceptable, water soluble polyhydroxy thermoprotecting agent, the aqueous suspension having particle size stability during steam sterilization such that the increase in volume weighted mean particle size during steam sterilization is not more than about two-fold, the method comprising sealing in a vial under nitrogen atmosphere, a composition comprising water, particles of a water insoluble or poorly soluble biologically active substance, one or more surface modifiers, and a pharmaceutically acceptable, water soluble polyhydroxy thermoprotecting agent, and steam sterilizing the suspension in the vial.

59. The method of claim 58, wherein the one or more surface modifiers are natural phospholipids or synthetic phospholipids.

60. The method of claim 58, wherein the ratio of the amount of the biologically active substance to the surface modifier is from 1:1 to 5:1.

61. The method of claim 58, wherein the polyhydroxy thermoprotecting agent is selected from the group consisting of trehalose, lactose, dextrose, sorbitol, dextran, mannitol, and mixtures thereof.

62. The aqueous suspension prepared by the method of claim 58.